

### **DETAILED ACTION**

The preliminary amendment filed on 1 June 2005 in which claims 1-34 were cancelled, and claims 35-68 were newly added, is acknowledged.

#### ***Priority***

This application is a National Stage entry of PCT/EP03/13622 filed on 3 December 2003 and claims priority to Germany foreign application 10256558.9 filed on 4 December 2002. A certified copy of the foreign priority document in German has been received. No English translation has been received.

#### ***Information Disclosure Statement***

The information disclosure statement (IDS) dated 1 June 2005 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609, except where noted. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

References B1, B2 and B3 were not considered because a translation of the document was not provided to the Office.

#### ***Election/Restrictions***

Applicant's election with traverse of Group I, claims 35-53 and 68, drawn to an aldonic acid ester of polysaccharides or polysaccharide derivatives in the reply filed on 29 September 2008 is acknowledged. It is also noted that Applicants indicate that they

elect the compound of Example 5 for an election of species. However, the Office Action dated 26 June 2008 did not require an election of species. As such, the full scope of the invention will be examined.

Upon further evaluation of the invention of Group I, further restriction of the claims is required. The restriction requirement dated 26 June 2008 has been modified as follows: claims 35-53, drawn to an aldonic acid ester of polysaccharides or polysaccharide derivatives will remain in Group I; claim 68, drawn to a pharmaceutical active ingredient coupled to polysaccharides or polysaccharide derivatives, will be put in new Group III.

During a telephone conversation with Mr. Steven Davis on 20 November 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 35-53. Affirmation of this election must be made by applicant in replying to this Office action. Mr. Steven Davis indicated that the traversal, as indicated in the response filed on 29 September 2008, is maintained in this requirement for further restriction.

The traversal is on the ground(s) that the Sommermeyer *et al.* reference do not teach an aldonic acid ester of a polysaccharide. It is noted that the Applicant has submitted Exhibits A, B and C to attest to the fact that the compound formed in the Sommermeyer *et al.* reference, that resulting from oxidized starch and a hydroxylamine, would result in a compound that is not commonly known as an ester. This is not found persuasive because as indicated in the Applicant's own specification, on p. 9,

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“[a]lcohols are employed to prepare the aldonic acid esters of the invention” and further goes on to say that “[t]he term alcohol includes compounds which have HO groups...[that] may be bonded inter alia to a nitrogen atom or to a phenyl radical”.

The requirement is still deemed proper and is therefore made FINAL.

Claims 54-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 29 September 2008.

Claims 35-53 will be examined herein.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of a “derivative” in these claims renders the claims herein indefinite. The recitation of “polysaccharide derivatives” and “starch fraction derivatives” is not clearly defined in the specification. **It is noted that on page 7, paragraph 2 of the specification, applicant indicates that “[i]t is additionally possible to employ derivatives of polysaccharides...[and] these include in particular hydroxyalkyl starches, for example hydroxyethyl starch and hydroxypropyl starch”.** However,

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this definition is not sufficient because it does not set forth the metes and bounds of the term "derivative". The 10<sup>th</sup> edition of the Merriam-Webster's Collegiate Dictionary (Merriam-Webster Incorporated: Springfield, Massachusetts, 1993, pp 311) defines "derivative" as, "a chemical substance related structurally to another substance and theoretically derivable from it." Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to **"polysaccharide derivatives"** or **"starch fraction derivatives"** herein. Thus, it is unclear and indefinite as to how the "derivative" herein encompassed thereby.

The recitation "in the range of greater than 10 to 25 mol %  $\alpha$ -1,6-glycosidic linkages" renders claim 38 herein indefinite. It is unclear whether "greater than" refers to 10 to 25 mol % or whether it refers to 10 mol % with 25 mol % as the upper limit. In the first interpretation, the recitation can read on any mol % greater than 10 mol %, without any upper limit. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted on page 6, paragraph 2, of the specification that Applicants intend for the average degree of branching to be "in the range between >10 and 25 mol %." If this is the case, it is respectfully suggested that Applicants amend the claim language to appropriately reflect this range.

The recitation "MW" in claim 39, 40 and 42 renders the claims herein indefinite. Acronyms or abbreviations can be interpreted differently depending on the context and the art. For example, "EPA" can stand for "eicosapentaenoic acid" or it can be an abbreviation for the "Environmental Protection Agency". Thus, it is unclear whether "MW" refers to molecular weight, or whether it is an acronym or abbreviation for

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something else. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim, rather than use acronyms or abbreviations. If Applicants intend to use acronyms or abbreviations in the claims, it is respectfully suggested that the acronym or abbreviation first be spelled out along with the acronym where it is first used in a claim before use of the acronym or abbreviation in subsequent claims.

The recitation “MS” in claim 42 renders the claim herein indefinite. As indicated above, acronyms or abbreviations can be interpreted differently depending on the context and the art. Thus, it is unclear whether “MS” refers to molar substitution or multiple sclerosis, or whether it is an acronym or abbreviation for something else. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim, rather than use acronyms or abbreviations. If Applicants intend to use acronyms or abbreviations in the claims, it is respectfully suggested that the acronym or abbreviation first be spelled out along with the acronym where it is first used in a claim before use of the acronym or abbreviation in subsequent claims.

The recitation “the alcohol component of the aldonic acid ester is derived is N-hydroxysuccinimide and sulfo-N-hydroxysuccinimide” renders claim 47 herein indefinite. It is unclear how the alcohol component of the aldonic ester can be derived from two compounds both containing an alcohol moiety when there is only one ester present in the aldonic acid ester compound.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-38, 41, 43-46 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by WIPO publication WO 2002/080979 by Sommermeyer *et al* (of record, PG Pub No. US 2005/0063943 A1 used as English equivalent translation).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyl starch is coupled to the active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of C<sub>2</sub>:C<sub>6</sub> substitution in the range of 2 to 20 (paragraph 0134). When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

Sommermeyer *et al.* discloses in Example 2 (paragraph 0147) a compound wherein hydroxyethyl starch oxidized at the reducing end, is reacted with HSA in the

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presence of EDC, in water. This is further exemplified in Table 2 (p. 11). Although not explicitly indicated by Sommermeyer *et al.*, it is evidenced by Marder *et al.* (PTO-892, Ref. U) that when an acid (oxidized hydroxyethyl starch) is reacted with EDC, an O-acylisourea intermediate, containing an ester linkage (compound (1) of Figure 1), is formed. When this reaction takes place in the presence of HOBt, a different ester (as defined by Applicant on p. 9 of the Specification) is formed, that between the acid and the hydroxyl group of HOBt (see compound (5) in Figure 1).

It is noted that Sommermeyer *et al.* do not explicitly indicate that HES used is the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "Who Food Additives Series No. 5" (PTO-892, Ref. V), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's position that the HES described by Sommermeyer *et al.* is amylopectin degradation fractions.

Thus, the compound formed between HES and EDC or HOBt in water, disclosed in Example 2 and Table 2 by Sommermeyer *et al.*, anticipates claims 35-38, 43-46 and 49.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Section [0001]**

Claims 39, 40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al* (of record, PG Pub No. US 2005/0063943 A1 used as English equivalent translation) as applied to claims 35-38, 41, 43-46 and 49 above.

The teachings of Sommermeyer *et al.* were as described above in the claim rejections under 35 USC § 102.

Although Sommermeyer *et al.* do not explicitly teach an aldonic ester wherein the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is



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between 2 and 15, Sommermeyer *et al.* do teach that HES preferably has a ratio of C<sub>2</sub>:C<sub>6</sub> substitution in the range of 2 to 20 (paragraph 0134).

Furthermore, it is noted that Sommermeyer *et al.* do not explicitly teach starch fractions with an average branching of 5-10 mol%  $\alpha$ -1,6-glycosidic linkages or an average branching of greater than 10-25 mol%  $\alpha$ -1,6-glycosidic linkages as in instant claims 39 and 40. However, as evidenced in PG Pub No. US 2004/0157207 A1 (PTO-892, Ref. A), naturally occurring amylopectin has a degree of branching of approximately 4 mol % and that clusters and molecule sections of amylopectin exhibit a slightly higher degree of branching compared with the natural average degree of branching (paragraph 0016). Therefore, it is considered *prima facie* obvious that one of ordinary skill in the art would optimize conditions for an aldonic ester wherein the starch fractions have an optimal degree of branching.

As such, it is considered *prima facie* obvious to one of ordinary skill in the art that the starch fractions of the aldonic acid ester have an optimal C<sub>2</sub>/C<sub>6</sub> ratio of substituents on carbon atoms C<sub>2</sub> and C<sub>6</sub> of the anhydroglucoses and an optimal degree of branching  $\alpha$ -1,6-glycosidic linkages. See below for recitation of a section from MPEP § 2144.05 regarding the obviousness of optimization of ranges.

The following is a quotation of MPEP § 2144.05:

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is

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already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

## Section [0002]

Claims 47, 48 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (of record, PG Pub No. US 2005/0063943 A1 used as English equivalent translation) as applied to claims 35-38, 41, 43-46 and 49 above, further in view of chapter entitled “Zero-Length Cross-linkers” by Hermanson (PTO-892, Ref. W).

The teachings of Sommermeyer *et al.* were as described above in the claim rejections under 35 USC § 102.

Sommermeyer *et al.* do not explicitly teach an aldonic acid ester wherein the alcohol component is derived from N-hydroxysuccinimide or sulfo-N-hydroxysuccinimide, nor does Sommermeyer *et al.* teach solutions comprising the aldonic acid ester as instantly claimed.

Hermanson teaches that EDC, a popular carbodiimide used in conjugation of biological substances, is labile in the presence of water (p. 170, section 1.1, paragraph 1). In the aqueous solutions, the oxygen atom of water can act as a nucleophile. Thus, hydrolysis of the O-acylisourea intermediate is a major competing reaction (p. 170, section 1.1, paragraph 2). An alternative is to use EDC in the presence of sulfo-N-

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hydroxysuccinimide (sulfo-NHS). Forming a sulfo-NHS ester intermediate from the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2). Furthermore, EDC/sulfo-NHS-coupled reactions are highly efficient and usually increases the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3).

It is noted that the Sommermeyer *et al.* and Hermanson references do not teach a solution comprising the aldonic acid ester wherein the solution comprises not more than 0.5% by weight of water, or is an aprotic solvent. However, as Hermanson teaches that EDC conjugate is labile in the presence of water and thus can undergo hydrolysis, it would have been *prima facie* obvious that one of ordinary skill in the art, a chemist, would have the aldonic acid ester in an aprotic organic solvent such as DMF or DMSO, rather than in water, so as to avoid hydrolysis of the aldonic acid ester. Although discussed with a different carbodiimide, this point is further illustrated by Hermanson in saying that "active ester synthesis done...in an organic solvent...does not have the hydrolysis problems of water-soluble EDC-formed ester" (p. 178). It is commonly known among chemists that DMF is used as a substitute for water when an organic solvent is desired.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the

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teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2) and that this reaction usually increases the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3)..

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

### **Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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